

DATA EVALUATION RECORD

CAPHRA/DELTAMETHRIN

Study Type: OCSPP Non-Guideline; *In Vitro* Metabolism Kinetics

EPA Contract No. EP-W-16-018

Task Assignment No.: 32-3-013 (MRID 50600304)

Prepared for
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STUDY TYPE: OCSPP Non-guideline; *In Vitro* Metabolism Kinetics.

PC CODE: 097805

DP BARCODE: D448281

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TEST MATERIAL (PURITY): Deltamethrin technical (99.4%)

SYNONYMS: (S)-cyano(3-phenoxyphenyl)methyl (1R,3R)-3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Brown, S. (2018) Deltamethrin: a study to determine the kinetics of metabolism of deltamethrin in rat and human plasma, rat and human liver microsomes and rat and human liver cytosol; Final Report. Concept Life Sciences Dundee, Dundee Technopole, Dundee, United Kingdom. Laboratory Project ID: CXR1574-I Deltamethrin Amendment 1, May 31, 2018. MRID 50600304. Unpublished.

SPONSOR: Council for Advancement of Pyrethroid Human Risk Assessment, LLC (CAPHRA), c/o Consumer Specialty Products Association, Inc., 1667 K Street, NW, Suite 300, Washington DC.

EXECUTIVE SUMMARY: In a non-guideline, *in vitro* metabolism study (MRID 50600304), the apparent intrinsic clearance (CL_{int}) of deltamethrin (99.4% a.i.; Batch # 0902200301) was determined in human liver microsomes, liver cytosol, and plasma, as well as juvenile and adult rat liver microsomes, liver cytosol, and plasma (See Appendix; Source of test systems). The study was performed incubating human as well as juvenile (15-day and 21-day old) and adult (90-day old) Sprague-Dawley rat liver microsomes, liver cytosol, and plasma in the presence and absence of NADPH with 0.1-5.0 μ M deltamethrin. Liver microsomes and cytosols were incubated at 0.1 mg/mL; plasma was incubated at a dilution of 1:1000. The 1:1000 dilutions yielded protein concentrations of 0.046, 0.048, and 0.077 mg/mL for 15-day, 21-day, and 90-day old rat plasmas, respectively, and 0.079 mg/mL for human plasma. Reactions were stopped by the addition of bifenthrin (internal standard; 98.1% a.i.; Batch # PL09-0427). Metabolism in the presence of NADPH reflected both NADPH-dependent cytochrome P450 (CYP) metabolism and NADPH-independent carboxylesterase (CES) metabolism. In contrast, NADPH-free incubations measured only CES metabolism. Using these results, CYP-only metabolism was estimated by the difference between the two metabolic rates. Because CYP activity is not observed in liver

cytosol and plasma, only deltamethrin metabolism by CES enzymes was investigated in these compartments. Deltamethrin metabolism, measured as loss of deltamethrin in the samples, was determined by LC-MS/MS. The Michaelis constant (K_m) and maximum reaction rate (V_{max}) were determined using Michaelis-Menten kinetics and the apparent CL_{int} was calculated using the equation: $CL_{int} = V_{max} \div K_m$.

RESULTS: Deltamethrin was predominantly metabolized by CYP enzymes in the 90-day old (1.59 mL/min/mg), 21-day old (1.05 mL/min/mg), and 15-day old (0.41 mL/min/mg) rat liver microsomes (Appendix, Table 1). Total CL_{int} (CYP and CES enzyme activity) was greatest for the 90-day old rat liver microsomes and decreased with decreasing age (0.41-1.70 mL/min/mg). CL_{int} from rat liver CES enzymes were 4.4% and 8.9% of CYP enzymes in the 21-day and 90-day old rat liver microsomes, respectively; deltamethrin metabolism by CES enzymes was not detected in the 15-day rat liver microsomes. Conversely, in human liver microsomes, metabolism was entirely due to CES enzymes (0.94 mL/min/mg), with no metabolism attributed to the CYP enzymes.

Deltamethrin was also metabolized to a much smaller extent by CES enzymes in rat and human liver cytosol and rat plasma. Rates of deltamethrin metabolism were greatest in 90-day old rat liver cytosol (0.073 mL/min/mg), decreasing in both 21-day (0.063 mL/min/mg) and 15-day old (0.025 mL/min/mg) rat liver cytosols (Appendix, Table 2). Human liver cytosol (1.09 mL/min/mg) demonstrated a rate similar to human liver microsomes. Rates of deltamethrin metabolism were greatest in 90-day old rat plasma (18.5 mL/min/mL), decreasing in 21-day old rat plasma (6.79 mL/min/mL) and 15-day old rat plasma (2.91 mL/min/mL). Deltamethrin was not metabolized by human plasma (Appendix, Table 3).

COMMENTS: Deltamethrin metabolism was attributed primarily to the CYP enzymes present in rat liver microsomes but was shown to be attributable to CES enzymes in both human liver microsomes and cytosol. Deltamethrin metabolism in the CYP enzymes of rat microsomes increased with age. Deltamethrin metabolism by CES enzymes was observed to a lesser extent in all rat cytosol and rat plasma. No CES metabolism was noted in human plasma, but CES metabolism in human liver cytosol was similar to the rate observed in human liver microsomes.

APPENDIX:**Source of test systems:**

Rat: Liver tissue and plasma from 15-day, 21-day, and 90-day old Sprague-Dawley rats (Charles River Laboratories, Raleigh, NC) were shipped to the performing laboratory. Pooled liver microsomal and cytosolic fractions were prepared for each age group (Study Number CXR1572).

Human: Human liver microsomes (Lot # 38290) and cytosol (Lot # 38290) were purchased from Corning B.V. Life Sciences, Amsterdam, The Netherlands. Human plasma (Lot # BRH1076793) was purchased from Sera Laboratories International, Haywards Heath, West Sussex, UK.

TABLE 1 Deltamethrin Liver Microsomes Summary Kinetics

Species	Experiment Date	Replicates in experiment	NADPH	Vmax nmol/min/mg protein	Km μ M	Clint mL/min/mg
Rat 90 day	14-Apr-17	n=2	+	1.36	0.801	1.70
			-	0.109	0.763	0.143
			CYP only	1.22	0.764	1.59
Rat 21 day	11-May-17	n=2	+	0.588	0.539	1.09
			-	0.0660	1.42	0.0466
			CYP only	0.534	0.509	1.05
Rat 15 day	18-Apr-17	n=2	+	0.513	1.27	0.405
			-	None detected. ¹		
			CYP only	Assumed to be = +NADPH rate		
Human	03-May-17	n=2	+	3.40	3.81	0.892
			-	3.26	3.48	0.937
			CYP only	None present (inferred from data above)		

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TABLE 2 Deltamethrin Liver Cytosol Summary Kinetics

Species	Experiment Date	Replicates in experiment	NADPH	Vmax nmol/min/mg protein	Km μ M	Clint mL/min/mg
Rat 90 day	31-Mar-17	n=2	-	0.0684	0.933	0.0733
Rat 21 day	05-Apr-17	n=2	-	0.0809	1.29	0.0628
Rat 15 Day	07-Apr-17	n=2	-	0.0709	2.86	0.0248
Human	06-Apr-17	n=2	-	1.29	1.18	1.09

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TABLE 3 **Deltamethrin Plasma Summary Kinetics**

Species	Experiment	Replicates in experiment	NADPH	Vmax nmol/min/mL plasma	Km μM	Clint mL/min/mL
Rat 90 day	13-Mar-17	n=2	-	33.1	1.79	18.5
Rat 21 day	09-Mar-17	n=2	-	9.01	1.33	6.79
Rat 15 Day	06-Mar-17	n=2	-	3.55	1.22	2.91
Human	27-Feb-17	n=2	-	No metabolism detected		

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